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Sodium Phenobarbital In Prevention of Electroconvulsive Shock-Induced Disruption of Taste-Illness Association

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SODIUM PHENOBARBITAL IN PREVENTION OF ELECTROCONVULSIVE SHOCK-INDUCED DISRUPTION OF TASTE-ILLNESS ASSOCIATION

A Thesis Submitted to the Graduate Division in Partial Fulfillment of the Requirements for the Degree of Master of Science

By

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ABSTRACT

Male Holtzman rats injected with a toxic solution of lithium chloride (US) 30 minutes after drinking saccharin flavored water (CS) learned to avoid that taste upon subsequent encounter. Electroconvulsive shock (ECS) interpolated temporarily between the pairing of a novel taste (CS) and an induced gustatory illness (US) prevents the taste from being associated with the illness (Kral, 1971). The purpose of the present experiment was to determine if sodium phenobarbital pretreatment would protect the association of taste with illness, against the normally interfering effects of ECS in the interpolated intervention paradigm. This question was investigated with a 2 (sodium phenobarbital vs. saline) x 2 (ECS vs. sham shock) x 2 (conditioned vs. nonconditioned) x 2 (conditioning day vs. test day) analysis of variance design. Results suggest sodium phenobarbital pretreatment to be ineffective in preventing against ECS disruption of the taste-illness association. Conditioning of the taste aversion and ECS disruption occurred in both drug and nondrug groups.

INTRODUCTION

Margerison (1962) reported that nationally almost 50% of the low-level institutionalized mentally retarded population were also diagnosed as epileptic. There are many possible explanations for the apparent relationship between susceptibility to seizures and mental retardation. First, both conditions may be coincidental symptoms of the same injury to the brain (Lennox and Collins, 1945). Second, the seizures themselves may produce anatomic injury as a side effect, resulting ultimately in a diffuse mental deterioration (Pond, 1961). Third, the probable occurrence of seizures may interfere on a behavioral-experiential basis with intellectual development (Robinson and Robinson, 1965). A fourth possibility which is the rationale for this thesis was proposed by Kral (1972). He suggested that chronic epileptiform discharges, whether they reach seizure threshold or remain subconvulsive, may themselves produce a generalized mental retardation or learning disability.

The animal literature (Glickman, 1961), studying the effects of seizures artifically induced by electrical current passed through the brain (electroconvulsive shock) provided support to Kral's hypothesis. The violent discharge of neurons, of which the motoric convulsion is the visible manifestation, is considered to disrupt on-going neural processes responsible for the fixation of recent experience into long-term memory. Apparently, memories are maintained in a labile state for sometime after initial acquisition during which consolidation into a physiologically more enduring state takes place (Hebb, 1949). Before the consolidation process has been completed, the memory trace is vulnerable

to interactions of various types which interfere with normal CNS functioning (Glickman, 1961; McGaugh, 1966; Deutsch, 1969). Furthermore, recent research (Lee-Teng, 1969) had suggested that an overt convulsion is itself not a prerequisite to the induction of a retention deficit. Low intensity electric currents (subconvulsive), are equally disruptive when applied to the brain for extended durations (Alpernard and McGraugh, 1968).

In general, therefore, the animal literature supports Kral's (1972) hypothesis of a common casual mechanism for CNS stimulation resulting in convulsions or a lower threshold for convulsions, and a diffuse impairment in the ability to learn or remember. The etiology of epilepsy in humans is, of course, extremely varied and this is not to suggest that all individuals with convulsive disorders evidence mental retardation or vice versa. The relationship, when it is present likely depends upon the specifics of the convulsive etiology.

While little is known about learning processes at a physiological level, there is reasonable agreement at a conceptual level as to what sequential stages are required for learning to take place: (1) acquisition, during which new associations are formed; (2) retention, storage of acquired experience; (3) retrieval, selection and release of stored knowledge when appropriate (Waugh and Norman, 1965; Atkinson and Shiffrin, 1965; Bowe, 1967). Human behavioral studies have shown that as far as the mentally retarded are concerned, the major weak link in the learning process appears to be original acquisition, not one of retention or retrieval (Ellis, 1970; Belmont and Butterfield, 1969). Apparently, if the material is well learned, (acquisition), the retarded individual can retain it (retention) and recall it at some future time (retrieval), about as well as

intellectually normal individuals (Klausmeier, Feldhusen, and Check, 1959; Vergason, 1964; Belmont, 1966). This acquisition or association formation deficit in the retarded becomes particularly relevant to the present discussion of convulsive disorders in the light of evidence already obtained by Kral (1969) and Kral (1971). Using a unique paradigm involving taste-illness associations Kral has been able to show that ECS disrupts acquisition and not memory as had previously been supposed. The relevancy of this finding will now be discussed in detail.

Taste-Illness Associations and Interpolated ECS as Paradigms for Studying the Effects on Convulsive Activity on Learning

Immediate post-trial exposure to electronconvulsive shock (ECS) frequently results in retention deficits for learning that would otherwise have been acquired during that trial. Traditionally, ECS has always been administered sometime after the presentation of the to-be-associated events (post-association ECS). This was a standard feature of learning paradigms typically used in experiments with ECS. This feature was prerequisite since about all common laboratory learning paradigms involved associations between audiovisual-tactual stimuli, modalities which depend on near contiguity of presentation in order for association learning to occur. Garcia and Ervin (1968), however, had shown that taste aversions could be conditioned after a single pairing of a distinctive taste (conditioned stimulus, CS), with induced toxicosis (unconditioned stimulus, US) despite taste-illness intervals of up to several hours. The exceptionally long conditioned stimulus-unconditioned stimulus intervals (CS-US) peculiar to the paradigm of taste-illness conditioning suggested to Kral (1969) the possibility of employing ECS between to-be-associated events rather than after. In addition to providing another way in which the effects of ECS on learning could be studied, the interpolated ECS paradigm might provide otherwise unobtainable information regarding the nature of association formation. Kral (1969), Kral and Wilcoxon (1970), Kral (1971), and Kral (1972), have shown that interpolated ECS seems to act directly on the associative mechanism itself to prevent the acquisition of the taste-illness association, while CS and US events maintain an independent existence in memory.

Based on Kral's reasoning then, the general rationale for this research study is that seizure activity may in and of itself result in a generalized learning (association formation) disability or induced retardation. By making use of the conditioned taste-aversion paradigm, it has already been shown that ECS disrupts the learning process directly while events intended for association remain independently stored in memory. Since retarded children exhibit a propensity for convulsive disorders (Margerson, 1962) and evidence a deficit in the ability to acquire new associations not memory per se, a cause-effect relationship is hypothesized. An experiment was recently conducted in Kral's laboratory (personal communication) in which animals were given injections of the anti-convulsant drug, dilantin, prior to a taste aversion learning trial involving ECS interpolated during the CS-US interval. Pre-ECS treatment with this drug, significantly reduced the learning deficit ordinarily resulting from an electrically induced convulsion. This is a preliminary result requiring replication with the same as well as related drugs. It does, however, support the overall hypothesis that conditions resulting in convulsive disorders can cause a learning disability which can then be prevented through use of an anticonvulsant medication. This investigator intends to expand and replicate this initial study using the anti-convulsant drug, sodium phenobarbital, as the pretreatment for protection against ECS disruption. If sodium phenobarbital acts to prevent interference with normal association formation as dilantin apparently did, it will lend additional support to Kral's (1972) hypothesis that epilepiform discharges may be one cause of mental retardation in humans as well as suggest a possible avenue for clinical treatment of some forms of learning disabilities.

The purpose of the present experiment, therefore, is to determine if pretreatment with sodium phenobarbital will protect the association of taste with an illness against the normally interfering effects of interpolated ECS. The main hypothesis is that animals receiving sodium phenobarbital which then experienced ECS interpolated during the taste-illness interval will drink less flavored water (CS) on subsequent trials (evidence aversion) than a group treated identically except for exclusion of sodium phenobarbital.

Several sub-hypotheses can be formulated to describe the expected effects of conditioning, ECS and sodium phenobarbital per se on flavored water consumption:

1. Animals which experienced induced illness following the novel taste of flavored water will drink less flavored water on subsequent exposures than animals which did not experience illness following the novel taste (conditioned aversion and non-conditioned control groups).

2. Animals which received ECS midway between the novel taste and induced illness will drink more flavored water upon subsequent exposure than animals which received only sham shock (no current passed) during the taste-illness interval (ECS intervention control group).

3. Animals which do not experience illness following the novel taste of flavored water will drink equivalent amounts of flavored water upon later exposures regardless of whether they received sodium phenobarbital or saline pretreatment, ECS or sham shock, or any combination of the drug and shock treatments not associated with conditioning. However, since ECS has already been shown to have negligible effects on CS (taste) or US (illness) events independent of aversion conditioning (Kral, 1970, Kral 1971, Kral and Beggerly, 1973) an interaction would not be expected in non-conditioned

control groups regardless of pretreatment with sodium phenobarbital or saline. These two control groups were, therefore, not utilized in the present study for the sake of economy.

METHOD

Subjects Forty-two male Hotlzman albino rats weighing between 180-250 grams and approximately sixty days of age at the start of the experiment, were housed in individual cages under a 16-hr. light, 8-hr. dark cycle. The animals were fed Purina Rat Chow ad lib. throughout the experiment.

Apparatus A solution of sweet water (0.1% W/W sodium saccharin) was the conditioned stimulus (CS). The unconditioned stimulus (US) was gustatory illness induced by intraperitoneal injection of 0.5 M LiCl (10 ml/kg of body weight). Lithium chloride (LiCl) at this dosage is known to induce an intense but non-lethal illness which results in an aversion to the novel taste with which it is paired (Garcia and Ervin, 1968). The ECS was produced by an electroconvulsive shock generator similar to the one designed by Woodbury and Davenport (1952) except that a plate supply transformer with a 1000 Vac secondary was used. The circuit diagram of the shock apparatus is presented in Appendix A. A 80 milliamp current was delivered for a duration of 1.0 sec. across the animal's ear by means of alligator clip electrodes padded with saline soaked cotton. ECS at this intensity and duration has previously been shown to disrupt conditioning of a sweet water aversion induced by lithium chloride (Kral, 1971). Sodium phenobarbital at a dosage of 50 mg/kg was used as the main independent variable. The drug was dissolved in physiological saline at a concentration of 50 mg per ml. Sodium phenobarbital at this dosage had previously been shown in a pilot study to have no apparent affect on drinking behavior while in other research it strongly affected learning (Bindre and Reichert, 1966), in rats.

Procedure Animals, upon arrival, were assigned at random to individual

cages where they remained except when being weighed, injected or shocked. Weighing and injection occurred in the colony room. Animals were given water ad lib for the first 72 hr. after arrival to offset water deprivation which occurred during shipping. Water bottles were removed after this 72 hr. period and the animals were placed on a 15 min. per day water drinking schedule for the remainder of the experiment. While on schedule, animals drank from 50 ml. granulated cylinders fitted with drinking tubes to permit measurement of the quantity consumed. Animals were weighed 15 min. prior to their drinking period and water consumption was measured and recorded each day of the schedule.

Animals were weighed and given regular tap water for the first seven days of the schedule to accustom them to the 15 min. water drinking period. On days 8 through 12, animals were weighed and then one half of them were injected intraperitoneally with sodium phenobarbital and the other half with an equivalent volume by body weight of psysiological saline 15 min. prior to presentation of tap water. This five day period was to allow for habituation of sodium phenobarbital effects on water consumption.

Conditioning of the taste aversion occurred on day 13 of the schedule. Animals were injected with either sodium phenobarbital or saline 15 min. prior to the drinking period just as they had been on days 8 through 12. However, instead of tap water, the animals were given sweet water during the drinking period. Fifteen min. after drinking, the animals were removed from their cages, placed in a plastic carrying pan and received ECS or sham shock, and then immediately returned to rest. Fifteen min. after shock treatment, animals were injected with either LiCl or saline.

Individual group conditions on conditioning day were as follows:

1. PEL (sodium phenobarbital-ECS-LiCl)

2. PSL (sodium phenobarbital-sham-LiCl)

3. PSS (sodium phenobarbital-sham-saline)

4. SEL (saline-ECS-LiCl)

5. SSL (saline-sham-LiCl)

6. SSS (saline-sham-saline)

Group PEL received sodium phenobarbital injection, ECS, and LiCl injection. Group SEL received physiological saline injection, ECS, and LiCl injection. A comparison of groups PEL-SEL would indicate the effect of sodium phenobarbital on the normally deleterious effects of ECS on conditioning of a taste aversion. Group PSL received sodium phenobarbital injection, sham shock, and LiCl injection. Group SSL received physiological saline injection, sham shock, and LiCl injection. A comparison of these two groups would indicate if sodium phenobarbital itself affected conditioning, independent of ECS. A comparison of groups SEL and SSL would demonstrate the normal disruptive ECS effect on learning. Group PSS received sodium phenobarbital injection, sham shock, and physiological saline injection. Group SSS received physiological saline injection, sham shock, and physiological saline injection. A comparison of PSS and SSS would indicate the intrinsic effects of sodium phenobarbital on drinking, independent of conditioning and ECS. Other relevant two group comparisons will be presented in the results section.

During the next two days, 14 and 15, the animals were weighed, injected with either sodium phenobarbital or physiological saline according to group, and then given tap water during the drinking period. On the sixteenth day, animals were tested for aversion to sweet water and this concluded the schedule.

RESULTS

The group mean water and sweet water consumption scores over all days of the experiment are presented graphically in Figure 1. It can be seen that administration of sodium phenobarbital on day 8, increased tap water intake. Water consumption for the sodium phenobarbital groups remained elevated over the following six days indicating that the drug had a direct effect on drinking.

The group mean sweet water intake for all groups on conditioning and test days are graphically depicted in Figure 2. As was suggested in the water drinking scores of days 8 through 12 depicted in Figure 1, sodium phenobarbital appeared to directly increase sweet water intake on conditioning day 13. An initial difference in sweet water intake on conditioning day between the sodium phenobarbital and saline pretreatment groups would constitute a sampling error making any drug-nondrug group comparisons on test day invalid. Therefore, a simple randomized analysis of variance was performed over all groups on conditioning day intake scores to determine if a sampling error did exist. A summary table of this analysis of variance is presented in Table 1. The results were significant ($F(5/57 = 11.37, p. < 0.001$) evidencing the presence of a sampling error on conditioning day. Since the means depicted in Figure 2 suggest rather clearly that the sampling problem was between not within drug-nondrug groupings, two further analysis of variance were calculated for these groupings separately on conditioning day. The summaries of these analyses are presented in Table 2 and Table 3.

The nonsignificant variance analyses within the drug-nondrug groupings ($F\ 2/19 = .89\ p. < .05$, $F\ 2/19 = 2.31$, $p. < .05$ respectively) support the interpretation that a sampling error existed only between drug-nondrug groupings.

Further analysis of variance utilizing two factor mixed designs were performed separately for drug (Table 4) and nondrug groupings (Table 5) which provided error terms for the Duncan's Multiple Range Test (Table 6) used to make relevant two-group comparisons. Significance was set at the 0.05 level throughout. ECS, in the present experiment, was found to disrupt learning of a conditioned taste aversion in both drug and nondrug groups, PEL vs. PSL, and SEL vs. SSL, respectively. Comparisons suggests indirectly that sodium phenobarbital was ineffective as a preventive against ECS disruption. There was also a significant differance within the PSL vs. PSS and SSL vs. SSS comparisons indicating that learning of a taste aversion did occur in both drug and nondrug groups.

DISCUSSION

The purpose of this experiment was to determine if the normally disruptive effect of ECS on conditioning of a taste aversion (Kral, 1970) could be ameliorated by pretreating animals with sodium phenobarbital. In the present design, animal groups both receiving and not receiving sodium phenobarbital were compared on conditioning day, when group differences in sweet water drinking were not expected. These animal groups were also compared on test day, when group differences in sweet water consumption would reflect ECS induced interference with taste aversion conditioning and whatever influence sodium phenobarbital had on the degree of ECS disruption.

However, in the present study, analysis of variance indicated a significantly higher consumption of sweet water among drug, than nondrug groups on conditioning day. A review of previous literature (Goodman-Gilman, 1965, Grossman, 1967, Bindra-Reichert, 1967) where sodium phenobarbital was used with a variety of learning paradigms gave no indication of a powerful drug effect on water consumption per se. In the present study, therefore, the sampling error which existed between drug and nondrug on conditioning day, prevented a direct assessment of any influence that sodium phenobarbital might have had on the expected ECS disruption of learning.

A pilot study was carried out prior to the experiment proper to establish if the high dose of sodium phenobarbital selected would prevent the animals from being able to drink. Unfortunately, a comparison group was not used. Since the animals appeared to drink normally under the influence of sodium phenobarbital at a dose sufficient to prevent ECS induced tonic-clonic convulsions it

was decided to proceed with the main experiment.

On day eight of the main experiment the introduction of sodium phenobarbital coincided with increased water drinking scores which remained high and stable over the remaining four day period prior to conditioning day. In spite of the initial indications of an intrinsic drug effect on drinking it was decided to complete the experiment. The assumption was made that the observed drug effect on water drinking was learned not intrinsic and, therefore, might not be expected to generalize to the novel tasting sweet water on conditioning day. There was also the consideration of indirect evidence that could demonstrate the existence of an amelioration of ECS induced interference by sodium phenobarbital despite significant differences in conditioning day drinking scores between drug-nondrug groups. This would have been the case if within the experimental drug groups ECS would have had no significant disruptive influence on conditioning as contrasted with the previously demonstrated (Kral, 1970) and, therefore, predicted disruption within the nondrug group. The results indicated quite clearly, however, that while sodium phenobarbital at the dosage employed has a direct and presumably unlearned influence on consumption per se it did not completely prevent ECS induced interference with conditioning.

It remains an empirical question, therefore, as to the existence of a certain sodium phenobarbital dosage level that does not alter normal drinking patterns and yet acts to lessen the disruptive effect of ECS on learning. The results of the experiment have clearly indicated the necessary procedures to answer this question. The first step must now be to conduct a dose-effect investigation in which a wide range of sodium phenobarbital dosage groups would be compared with a nondrug control group

to establish their relative effects on drinking behavior only. The design employed in the current experiment could then be repeated employing the highest dosage of sodium phenobarbital that the dose-effect study indicated would not alter normal water intake. This procedure should eliminate the condtional day sampling error observed in the present experiment and allow the appropriate drug-nondrug group comparisons to determine if sodium phenobarbital can lessen the disruptive effects of ECS on taste aversion conditioning.

CONCLUSIONS

1. Sodium phenobarbital pretreatment under the present conditions and dosage suggests little influence in protecting the association of taste with illness, against the normally interfering effects of ECS in the interpolated intervention paradigm.

2. Sodium phenobarbital had the direct and presumably unlearned influence of increasing liquid consumption per se, independent of ECS or conditioning.

3. ECS disruption and conditioning of a taste-aversion and ECS disruption of the taste-illness association occurred under both drug and nondrug conditions.

Figure 1

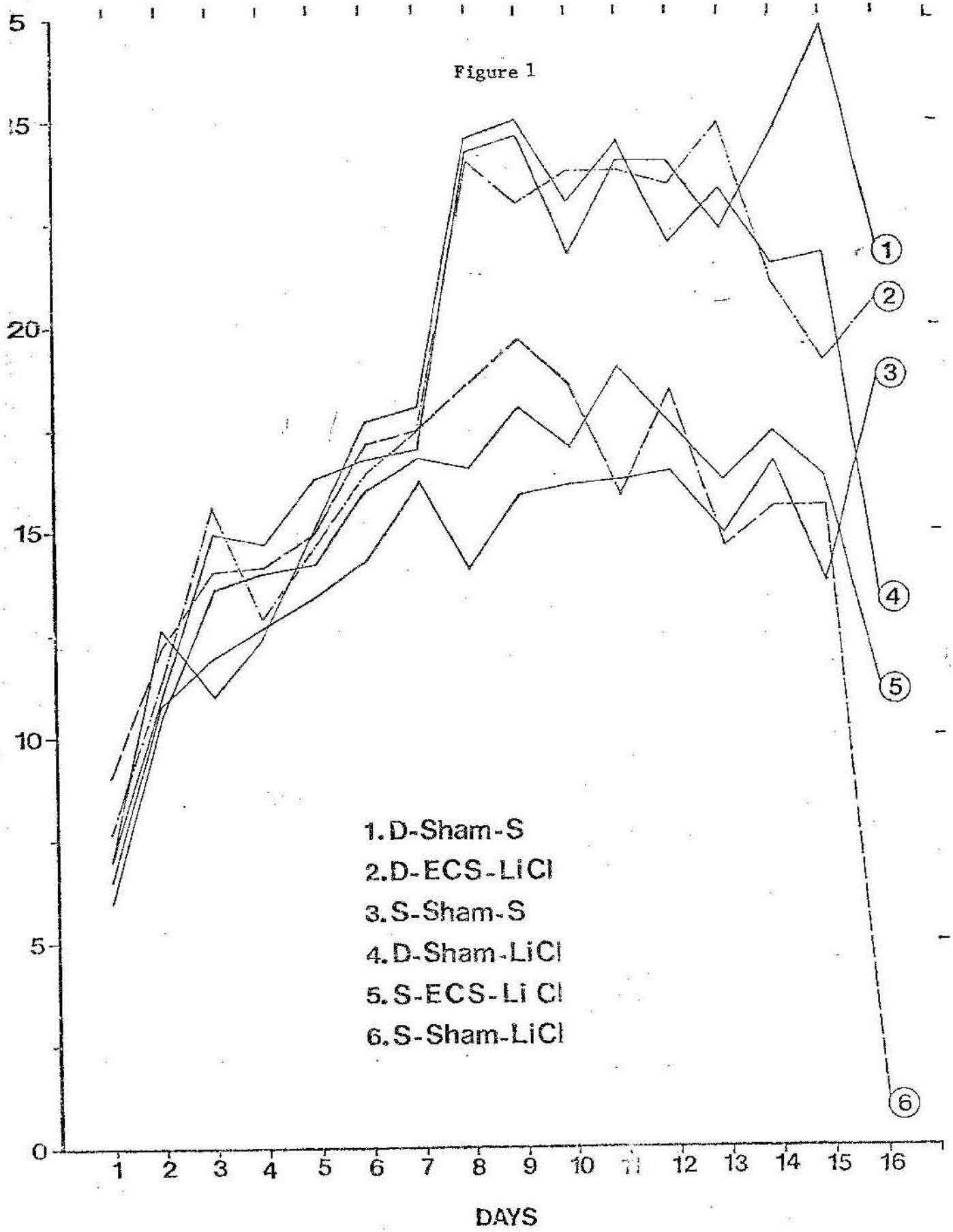

Fig. 1 Mean water and sweet water consumption for all groups over all days of the experiment.

Figure 2

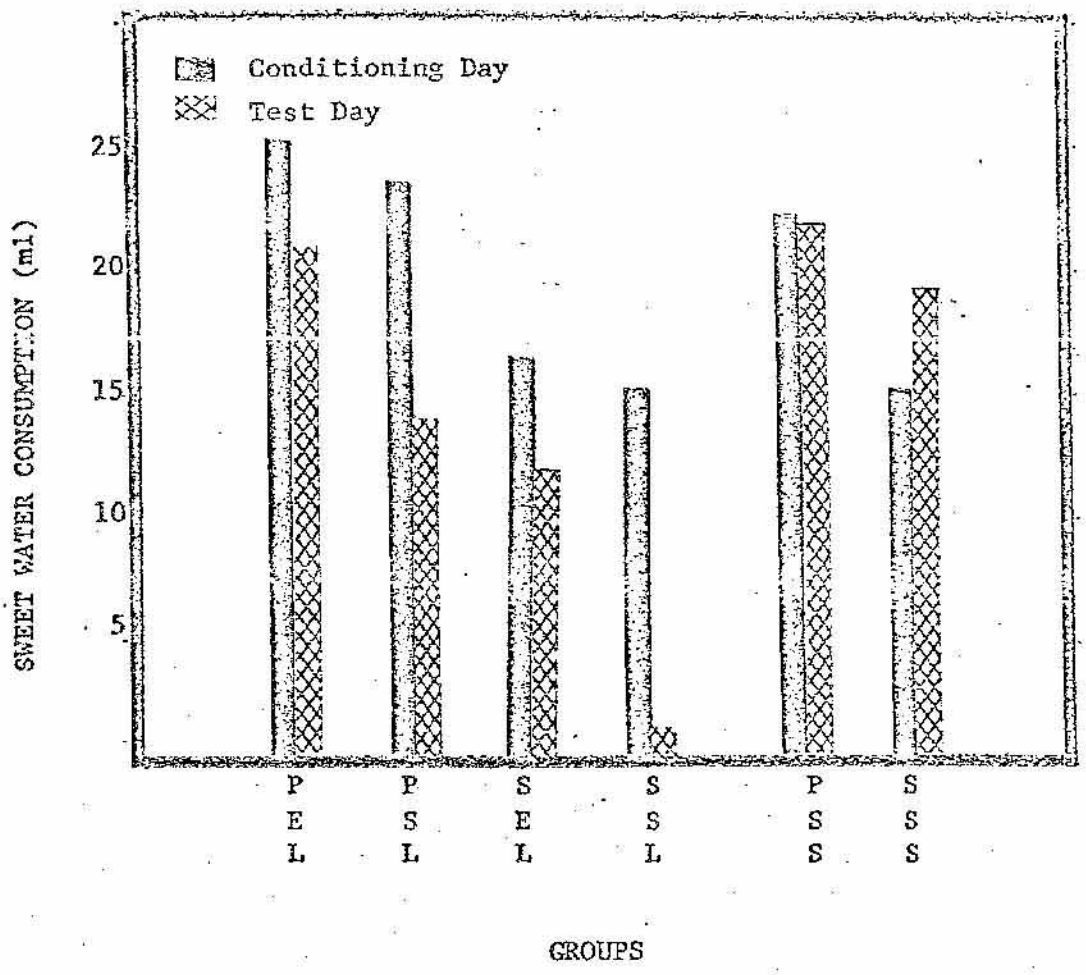

Fig. 2 Mean sweet water consumption for all groups. Sodium phenobarbital pretreatment did not ameliorate the disruptive effect of ECS on learning the taste-illness association.

TABLE I

ANALYSIS OF VARIANCE SUMMARY TABLE
FOR SWEET WATER CONSUMPTION ON
CONDITIONING DAY FOR ALL GROUPS

SOURCE	SS	df	MS	F	P
Total	1291.64	41			
Between subjects	782.50	5	156.50	11.37	.001
Within subjects	509.14	37	13.76		

TABLE II

ANALYSIS OF VARIANCE SUMMARY TABLE
FOR SWEET WATER CONSUMPTION ON
CONDITIONING DAY FOR NONDRUG GROUPS

SOURCE	SS	df	MS	F	P
Total	242.57	20			
Between subjects	10.57	2	5.29	2.31	n.s.
Within subjects	232.0	19	2.21		

TABLE III

ANALYSIS OF VARIANCE SUMMARY TABLE
FOR SWEET WATER CONSUMPTION ON
CONDITIONING DAY FOR DRUG GROUPS

SOURCE	SS	df	MS	F	P
Total	303.14	20			
Between subjects	26	2	13	.89	n.s.
Within subjects	277.14	19	14.59		

TABLE IV

ANALYSIS OF VARIANCE SUMMARY TABLE -- FOR SWEET WATER CONSUMPTION ON CONDITIONING AND TEST DAY FOR NON-DRUG GROUP

SOURCE	SS	df	MS	F	P
Total	1712.12	41			
Between subjects	766.62	20			
Conditions	560.34	2	280.17	24.45	.001
$Error_b$	206.28	18	11.46		
Within subjects	945.50	21			
Trials	242.88	1	242.88	24.34	.001
Trials X conditions	522.90	2	261.45	26.20	.001
$Error_w$	179.72	18	9.98		

TABLE V

ANALYSIS OF VARIANCE SUMMARY TABLE
FOR SWEET WATER CONSUMPTION ON
CONDITIONING AND TEST DAY FOR
DRUG GROUP

SOURCE	SS	df	MS	F	P
Total	1497.83	41			
Between subjects	714.33	20			
Conditions	152.91	2	76.46	2.45	n.s.
Within subjects	783.5	21			
Trials	242.88	1	242.88	11.54	.005
Trials X conditions	161.76	2	80.88	3.84	.05
$Error_w$	378.86	18	21.05		

TABLE VI

DUNCAN'S MULTIPLE-RANGE TEST COMPARISONS
SUMMARY TABLE FOR DRUG AND NONDRUG
GROUPS

TREATMENT	MEAN	COMPARISON TREATMENT	GROUP MEAN	M1-M2	R*	P
PEL	45.71	PSS	44.29	1.42	6.56	n.s.
PEL	45.71	PSL	37.00	8.71	6.27	0.05
PSL	37.00	PSS	44.29	7.29	6.27	0.05
SEL	27.43	SSS	33.29	5.86	3.98	0.05
SEL	27.43	SSL	15.71	11.72	3.80	0.05
SSL	15.75	SSS	33.29	17.58	3.80	0.05

* p. .05

Appendix B

Schedule of Operations

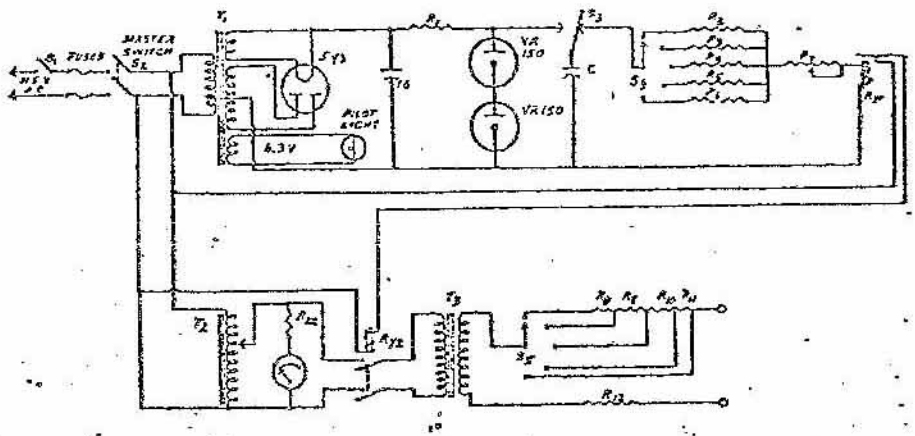

FIG. 1

Circuit diagram and parts for electroshock apparatus

S_1 Interlock switch on cabinet door.
S_2 Master Switch.
S_3 Push button to initiate timer; normally connected to timer.
S_4 Timer switch 5 pole, single circuit wafer type.
S_5 Current range switch, porcelain base, high voltage.
T_1 Small replacement type transformer 350-0-350 volts.
T_2 Variable autotransformer, 3 ampere capacity.
T_3 Plate supply transformer, primary 110 volts, secondary 1000 volts, 200 ma.
C Timer condenser, 5 mfd, 1000 volts.
Ry_1 Sensitive relay, 10,000 ohm winding.
Ry_2 Heavy duty, double pole relay or contactor, 110 volt coil.
R_1 Adjust to give 25-30 ma through regulator tubes; approximately 2,000 ohms 10 watts.
R_2-R_6 Select to give desired time of closure.
R_7 Adjust to give slight changes in timing of all timing positions.
R_8-R_{12} Wire wound, 100 watt variable resistors with sliding taps. Adjust to give desired full scale current. The following values are approximate.
R_8 120,000 ohms
R_9 40,000 ohms
R_{10} 20,000 ohms
R_{11} 16,000 ohms
R_{12} 4,000 ohms
Meter: (Indicated by circle-enclosed arrow in lower left part of diagram.) Any meter capable of reading rms *a-c* volts; scale may be hand-calibrated to give desired current ranges.

SCHEDULE OF OPERATIONS
SQUAD A

T = TIME CHANGE (min.) S = SALINE P = PLACE WATER BOTTLE
I = INJECT D = DRUG R = READ WATER BOTTLE

T	Operation		T	Operation		
1	I 1	S	22	I 22D	P7	
2	I 2	S	23	I 23D	P8	
3	I 3	S	24	I 24D	P9	
4	I 4	S	25		P10	
5	I 5	S	26		P11	
6	I 6	S	27		P12	
7	I 7	S	28		P13	
8	I 8	S	29		P14	
9	I 9	S	30		P15	
10	I 10	S	31		P16	R1
11	I 11	S	32		P17	R2
12	I 12	S	33		P18	R3
13	I 13	D	34		P19	R4
14	I 14	D	35		P20	R5
15	I 15	D	36		P21	R6
16	I 16D	P1	37		P22	R7
17	I 17D	P2	38		P23	R8
18	I 18D	P3	39		P24	R9
19	I 19D	P4	40			R10
20	I 20D	P5	41			R11
21	I 21D	P6	42			R12

SQUAD A

T = TIME CHANGE (min.) S = SALINE P = PLACE WATER BOTTLE
I = INJECT D = DRUG R = READ WATER BOTTLE

T	Operation	T	Operation
43	R13	65	SHAM20 I5 LiCl
44	R14	66	SHAM21 I6 LiCl
45	R15	67	SHAM22 I7 LiCl
46	R16 ECS1	68	SHAM23 I8 LiCl
47	R17 ECS2	69	SHAM24 I9 SAL
48	R18 ECS3	70	I10 SAL
49	R19 ECS4	71	I11 SAL
50	R20 SHAM5	72	I12 SAL
51	R21 SHAM6	73	I13 LiCl
52	R22 SHAM7	74	I14 LiCl
53	R23 SHAM8	75	I15 LiCl
54	R24 SHAM9	76	I16 LiCl
55	SHAM10	77	I17 LiCl
56	SHAM11	78	I18 LiCl
57	SHAM12	79	I19 LiCl
58	ECS13	80	I20 LiCl
59	ECS14	81	I21 SAL
60	ECS15	82	I22 SAL
61	ECS16 I1 LiCl	83	I23 SAL
62	SHAM17 I2 LiCl	84	I24 SAL
63	SHAM18 I3 LiCl		
64	SHAM19 I4 LiCl		

SCHEDULE OF OPERATIONS
SQUAD B

T = TIME CHANGE (min.)
I = INJECT
S = SALINE
D = DRUG
P = PLACE WATER BOTTLE
R = READ WATER BOTTLE

T	Operation	T	Operation
1	I 1 S	22	P7
2	I 2 S	23	P8
3	I 3 S	24	P9
4	I 4 S	25	P10
5	I 5 S	26	P11
6	I 6 S	27	P12
7	I 7 S	28	P13
8	I 8 S	29	P14
9	I 9 S	30	P15
10	I 10 D	31	P16 R1
11	I 11 S	32	P17 R2
12	I 12 S	33	P18 R3
13	I 13 S	34	R4
14	I 14 S	35	R5
15	I 15 S	36	R6
16	I 16 S P1	37	R7
17	I 17 S P2	38	R8
18	I 18 S P3	39	R9
19	P4	40	R10
20	P5	41	R11
21	P6	42	R12

SQUAD B

T = TIME CHANGE (min.) S = SALINE P = PLACE WATER BOTTLE
I = INJECT D = DRUG R = READ WATER BOTTLE

T	Operation			T	Operation	
43	R13			65	I5	LiCl
44	R14			66	I6	LiCl
45	R15			67	I7	SAL
46	R16	ECS1		68	I8	SAL
47	R17	ECS2		69	I9	SAL
48	R18	ECS3		70	I10	LiCl
49		SHAM4		71	I11	LiCl
50		SHAM5		72	I12	LiCl
51		SHAM6		73	I13	LiCl
52		SHAM7		74	I14	LiCl
53		SHAM8		75	I14	LiCl
54		SHAM9		76	I16	SAL
55		ECS10		77	I17	SAL
56		ECS11		78	I18	SAL
57		ECS12				
58		SHAM13				
59		SHAM14				
60		SHAM15				
61		SHAM16	I1 LiCl			
62		SHAM17	I2 LiCl			
63		SHAM18	I3 LiCl			
64			I4 LiCl			

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